

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): DODDA MOHAN RAO et al.

Serial No: 10/524,478

Group Art Unit: 1626

Filed: 02-11-2005

Examiner: LOEWE, SUN JAE Y

Att. Docket No.: S2096/20001

Confirmation No.: 6950

For: NOVEL CRYSTALLINE FORM OF LINEZOLID

FIRST DECLARATION OF D. MOHAN RAO, PH.D. UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, D. Mohan Rao, a citizen of India, hereby declare and state:

1. I am a co-inventor of the subject matter described and claimed in the present application.

2. I am the Managing Director of Symed Laboratories Limited, with more than 25 years of experience in the Pharmaceuticals Industry. The resume attached as **Appendix 1-A** accurately reflects my professional credentials.

3. I have reviewed the present application and its prosecution history including the Office Action of March 19, 2009.

4. I understand from my review of the Office Action in this case that claim 1 stands rejected under 35 U.S.C. § 102(b) and/or 35 U.S.C. 103(a) as being anticipated by and/or obvious over Barbachyn et al., Meng, and Pearlman et al.

5. I understand from my attorneys that 35 U.S.C. § 102(b) provides:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States[.]

6. I understand from my attorneys that for a prior art reference to anticipate the claims, the reference must teach every element of the claims.

7. I understand from my attorneys that 35 U.S.C. § 103(a) provides:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

8. While I am not an expert in patent law, my experience and educational background enable me to render an informed opinion as to the facts underlying the determination of obviousness, including: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results. For the reasons discussed below, I believe that the facts support a conclusion that the claims are not obvious over the cited references.

9. According to my attorneys, finding obviousness requires that the prior art reference (or references when combined) must teach or suggest all the claim limitations and that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

10. The present application claims a crystalline linezolid form III, characterized by an x-

ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees, and further characterized by an IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm^{-1} , wherein there is at least a 99.8% enantiomeric excess of the linezolid form III.

11. The Examiner argues that that IR data is insufficient to unambiguously distinguish different polymorphic forms.

12. I have carefully reviewed Barbachyn et al., Meng, and Pearlman et al.

13. It is my opinion that the methods as disclosed in the Barbachyn et al., Meng, and Pearlman et al. references would not produce the claimed linezolid polymorphic form III, based on a comparison of the DSC thermogram for the claimed linezolid polymorphic form III, the DSC thermogram for linezolid polymorphic form II, and the art reported melting temperature of linezolid.

14. Using the methods described in the application, I and/or researchers under my direct supervision prepared linezolid polymorphic form III, and evaluated the linezolid polymorphic form III using differential scanning calorimetry (DSC). The DSC thermograph was obtained using a TA Instruments DSC Q200 instrument at a scan rate of $10.00^\circ\text{C}/\text{min}$ over a temperature range of $40\text{--}220^\circ\text{C}$.

15. The DSC thermogram of linezolid polymorphic form III is attached as **Appendix 1-B**.

16. The linezolid polymorphic form III DSC thermogram has an endothermic peak (i.e., melting temperature) at 178.96°C .

17. In addition, I and/or researchers under my direct supervision prepared linezolid polymorphic form II, and evaluated the linezolid polymorphic form II using differential scanning calorimetry (DSC).

18. The DSC thermogram of linezolid polymorphic form II is attached as **Appendix 1-C**.

19. The linezolid polymorphic form II DSC thermogram had endothermic peaks at 155.32 °C and 179.06°C, and an exothermic peak at about 159°C.

20. Accordingly, I believe that the facts support a conclusion that the methods as disclosed in the Barbachyn et al., Meng, and Pearlman et al. references would not produce the claimed linezolid polymorphic form III, based on a comparison of the DSC thermogram for the claimed linezolid polymorphic form III, the DSC thermogram for linezolid polymorphic form II, and the art reported melting temperature of linezolid.

21. None of the cited references (alone or in combination) describes the claimed linezolid polymorphic form III, and therefore lack teaching or suggestion of all the claim limitations.

22. Further, following the cited references, one of ordinary skill in the art would have lacked motivation to use these references to make the claimed linezolid polymorphic form III of the present invention with a reasonable expectation of success because such motivation to modify the reference(s) is not present. Absent such reasonable motivation, the present invention would not have been obvious to a person of ordinary skill in the art in light of the cited references.

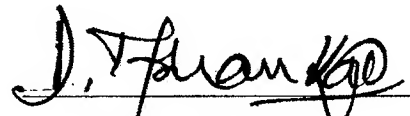
23. Accordingly, since Barbachyn et al., Meng, and Pearlman et al. does not teach every element of the claims, the claims are not anticipated.

Application No. 10/524,478
Declaration Under 37 C.F.R. § 1.132

24. In addition, since Barbachyn et al., Meng, and Pearlman et al. (alone or in combination) do not teach or suggest every element of the claims, the claims are not obvious.

25. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 3/06/2009


D. Mohan Rao, Ph.D.

Appendix 1 - A

RESUME

Name : Dr. D.MOHAN RAO

Date of Birth : 11.04.1958

Educational Qualifications : Master of Science (Organic Chemistry), Regional Engineering College, Warangal, Andhra Pradesh, India
Ph.D in Organic Chemistry from Kakatiya University
Andhra Pradesh, India

Area of Research : Heterocyclic Chemistry – Specific to the synthesis and activity of Haloquinolones

Details of Papers Published : Published 6 papers on different Subjects related to Heterocyclic Chemistry.

Details of Patents : 4 Patents are filed in EUROPE, U.S and INDIA.

Industrial Experience : 25 years of Industrial Experience

1982-1984 – Research Chemist – Standard Organics Limited, Hyderabad, Andhra Pradesh India

1984-1985 – Research Chemist – Standard Research Centre, Hyderabad, Andhra Pradesh India

1985-1991 - Scientist, Cheminor Drugs Limited, Dr.Reddy's Group, INDIA

1991-1998 - Sr.Vice President, Scientific and Regulatory Affairs, Cheminor Drugs Limited, Dr.Reddy's Group, INDIA

Since 1998 - Managing Director, Symed Labs Limited, Hyderabad, Andhra Pradesh, INDIA

SUMMARY OF PROFESSIONAL EXPERIENCE:

Gained expertise in developing and commercialisation of processes, which are both novel and cost-effective. Invented new polymorphs and new processes for the preparation of Linezolid (which is latest Anti bacterial) and filed patents in EUROPE, US and INDIA. Gained expertise in interpretation of the Regulatory Requirements with respect to the Active Pharmaceutical Ingredients. As Sr. Vice President (Scientific and Regulatory Affairs), Responsible for Regulatory submissions and the approval of different products of M/s. Cheminor Drugs Limited by the US FDA. Involved in the submissions of the Dossiers for the Certification of Suitability for European Pharmacopoeia for a few products.

Acquired hands-on experience in analytical method development and validation and well versed in handling of different instruments such as IR, UV, HPLCs, GCs, DSC etc. and gained expertise in the interpretation of Mass and NMR spectroscopy as well as X-Ray Diffraction techniques.

List of Publications:

- 1) Aflatoxin Analogues as possible Anticoagulants.
T. Giridhar, D. Mohan Rao and R.B. Reddy J. Heterocyclic chem. 33,5(1996).
- 2) Synthesis and Reactions of 4H-Imidazo[4,5-e] [2.1.3] Benzothiadiazol-5(6H)-one
Dodda Mohan Rao, Thota Giridhar, Gunapati Venkateshwara Prasad, Reguru Buchi Reddy and Garimella Venkata Padmanabha Chandra Mouli Hetero cycles, Vol 45, No.1, 1997.
- 3) A NOVEL SYNTHESIS OF BENZOTHIAZEPINES
D. Mohan Rao, T. Giridhar, R.B. Reddy and G.V.P. Chandra Mouli Indian Journal of Heterocyclic chemistry Vol.5 Oct-Dec. 1995, PP 145 -146.
- 4) Studies on haloquinolines: Part I-Synthesis and Characterisation of substituted halo quinolines
D. Mohan Rao, T. Giridhar and R.B. Reddy Indian Journal of chemistry Vol.36 B, January 1997, PP.29-32.
- 5) Synthesis and Antimicrobial properties of 2- Substituted Mercapto-4,8-Dimethyloxazolo(4,5-C) Quinolines.
S. Sudhakar, G.V.P. Chandra Mouli, T. Giridhar, D. Mohan Rao and R.B. Reddy Asian Journal of Chemistry Vol 8 No. 3 (1996), 438-442.
- 6) Synthesis and Antimicrobial Activity of 2-Aryl -1-Methyl-3H-1,4-Oxazino(5,6-C) Quinolines.
S. Sudhakar, G.V.P. Chandra Mouli, T. Giridhar, D. Mohan Rao and R.B. Reddy Asian Journal of Chemistry Vol 8 No.3 (1996), 459-462.

List of Patents:

- 1) A Novel Crystalline form of Linezolid.

International Publication Number : WO 2005/035530 A1.

- 2) A Novel process for the preparation of Linezolid and related compounds.

International Publication Number : WO 2005/099353 A2.

- 3) Novel intermediates for Linezolid and related compounds.

International Publication Number : WO 2006/008754 A1.

- 4) A Novel Amorphous Form of Linezolid.

International Publication Number : WO 2007/026369 A1.

- 5) Process for preparation of substantially Optically pure Levo rotatory and Dextro rotatory Enantiomers of Cetirizine using Novel Intermediates.

International Application Number : WO2008/152650 A1.

Date :

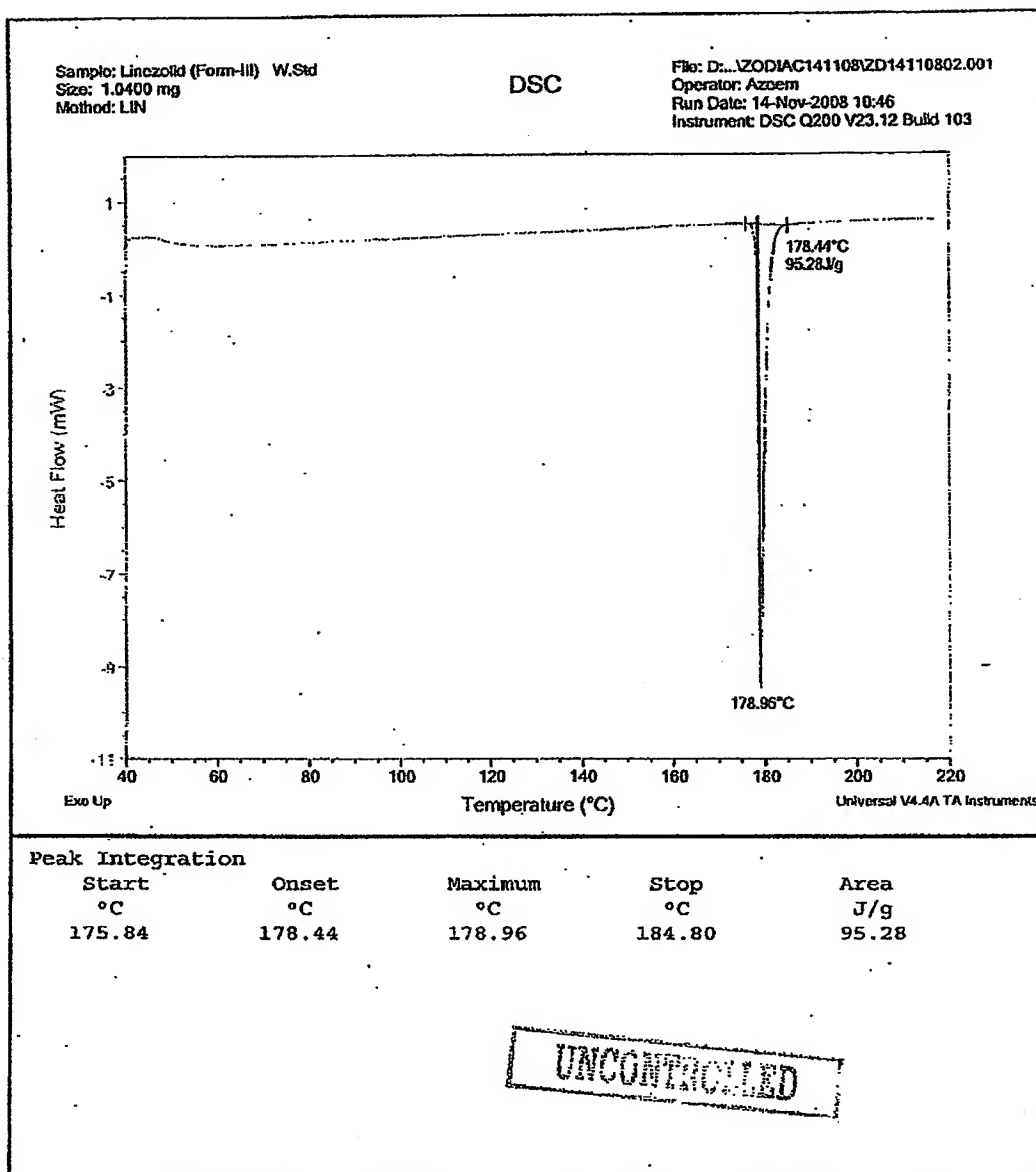
Place :

(Dr.D.Mohan Rao)

Appendix 1 - B

SYMED LABS LIMITED

Linezolid (Form-III) DSC REPORT



Method Log:

- 1: Equilibrate at 40.00°C
- 2: Ramp 10.00°C/min to 220.00°C
- 3: Air cool: On
- 4: End of method

Analysed by:
 Date:

[Signature]
 14-11-08

Checked by:
 Date:

[Signature]
 14-11-2008

Appendix 1 - C

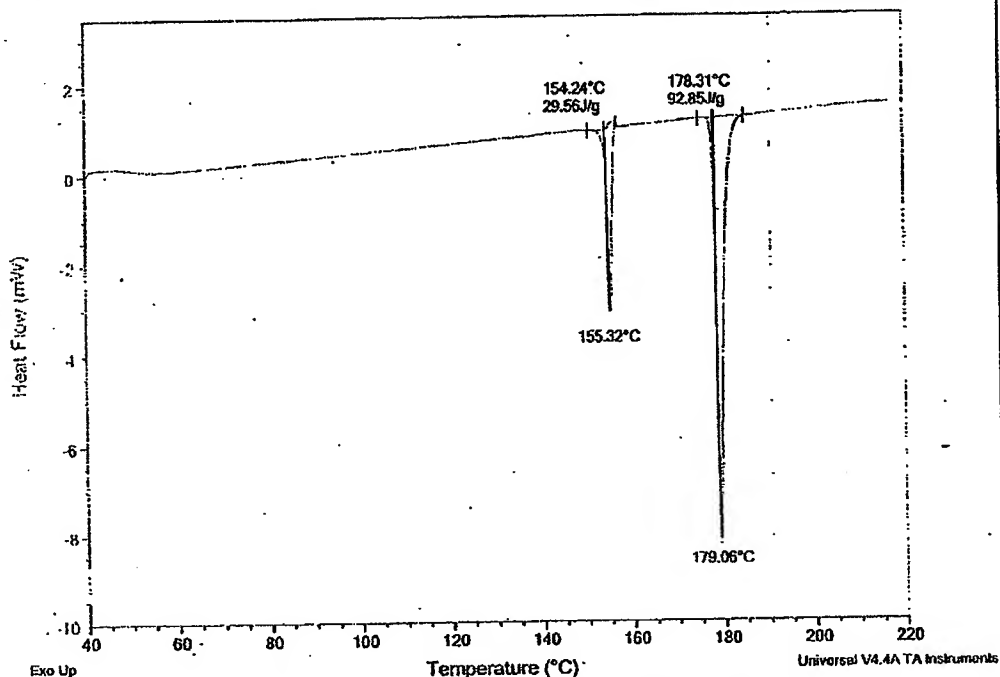
SYMED LABS LIMITED

Linezolid (Form-II) DSC REPORT

Sample: Linezolid (Form-II) W.Std
Size: 1.1700 mg
Method: LIN

DSC

File: D:\ZODIAC\151108\ZD15110802.001
Operator: Azeem
Run Date: 15-Nov-2008 15:47
Instrument: DSC Q200 V23.12 Build 103



Peak Integration

Start °C	Onset °C	Maximum °C	Stop °C	Area J/g
150.54	154.24	155.32	156.85	29.56
174.99	178.31	179.06	184.80	92.85

UNCONTROLLED

Method Log:

- 1: Equilibrate at 40.00°C
- 2: Ramp 10.00°C/min to 220.00°C
- 3: Air cool: On
- 4: End of method

Analysed by:
Date:

[Signature]
15-11-08

Checked by:
Date:

[Signature]
15-11-2008